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This is a communication from the examiner in charge of your application.
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☒ This application has been examined ☐ Responsive to communication filed on _____ ☐ This action is made final.

A shortened statutory period for response to this action is set to expire three (3) month(s), 0 days from the date of this letter. Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☒ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☒ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-22 are pending in the application.

   Of the above, claims none are withdrawn from consideration.

2. ☐ Claims _____ have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-22 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☒ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

The application should be reviewed for errors. The following is a sample of the informalities found. The status of the parent applications listed in the first paragraph of the specification at page 1 should be updated. It is suggested that the entire application be reviewed for completeness and accuracy of the cited bibliographic information of the cited references (note the "Moossor" at page 1, line 21 should be "Moossa") which should for uniformity be cited using a single bibliographic format. The line spacing as for example at page 12, lines 23-31 and at page 11, lines 25-32 do not meet the criteria set forth in 37 CFR 1.52 (b), see also MPEP 608.01. Corrections are required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. 112, first paragraph, as failing to provide an adequate written description for practicing the claimed invention.

At page 4, line 13-15, the definition of "therapy-sensitizing gene" is incorrect as it defines same as a gene product. A gene product is not a gene and the instant specification does not demonstrate how a gene product as for example, the p53 protein, is a gene (a DNA polymer encoding a specific product).

At page 5, lines 29+, the specification indicates that "wild-type therapy-sensitizing gene activity" means the activity in a normal non-neoplastic cell and specifically is stated to mean "the ability of the protein or portion of the protein encoded by the therapy-sensitizing gene to sensitize a tumor cell to cancer therapy". This is also incorrect as the activity of the protein is not the activity of the DNA nor does the instant specification appear to demonstrate what part of the DNA encodes the "activity" of the protein. In the paragraph starting at line 23 of page 6, the definition of tumor cell is inaccurate in view of the Dictionary of Microbiology and Molecular Biology which at page 591 indicates tumor (page 920) is a neoplasia wherein the cells have uncontrolled cell division that results in an abnormal growth, it does not appear to, *per se*, refer to cells which are "capable of" as all cells are capable of undesired proliferation. Note that Stedman's Medical Dictionary (see page 245) also defines carcinoma cells

(cancer/tumor cells) not as cell which are "capable of" but cells which display specific characteristic phenotypic properties. Thus, the definition at page 6 is inaccurate as "capable of" does not indicate in a positive manner that "undesired proliferation or abnormal persistence, or abnormal invasion of tissues" is displayed by these cells but only that they are capable of, and, "capable of" does not distinguish cancer cells from any other cell.

The paragraph bridging pages 6-7 of the specification refers to determining the therapy sensitizing portion" of the protein. It does so by indicating that one needs to experiment wherein the Unger *et al.* (Molec. Cell. Biol., vol 13) reference only refers to the DNA encoding p53 and does not demonstrate the present specification page 4-6 discussion as to finding any other prospective candidate genes that have "therapy sensitizing" function. Where certain references are cited, the specification in the above indicated paragraph does not *per se* indicate how to *a priori* determine same but for experimentation and the discussion at pages 8-13 do not demonstrate how to extrapolate the teachings regarding p53 to other proteins or DNA (such as the DNA encoding the Fas gene product (see claim 21 and page 8, wherein the *fas* gene is not even defined in the instant specification)) especially where the instant written description in the sentence bridging pages 9-10 indicates that "Expression of wild-type p53 does not affect the growth properties of some tumor cell lines ...". In fact Chen *et al.* (Oncogene, vol. 6) explicitly indicate (page 1799) that even when DNA encoding p53 is expressed, it is apparently ineffective in altering the neoplastic properties of the cell and that the effect of p53 may in fact be dependent upon cell type - i.e., that the effect may be cell type specific and therefore not effective in all types of tumor cells - thus, there is doubt created in the art that the DNA encoding p53 would be effective in all cancers - what effect does the DNA encoding p53 and p53 have on retinoblastoma when the defect is in the DNA encoding the Rb protein? Here, the specification in the paragraph bridging pages 9-10 indicates that not all mutations in the DNA encoding p53 have significant down regulation of proliferation by wild-type p53 expression and that "expression of wild-type p53 does not affect growth properties of some tumor cell lines, including human papillomavirus-expressing cell lines, and A673 rhabdomyosarcoma cells" - i.e., here the specification creates its own doubt as to the predictability of the using even the DNA encoding p53 in treating all types of cancers and cancer cells because the effect is from the specification apparently variable (note the last sentence of the paragraph bridging pages 9-10) and where the effect is apparently variable *in*

vitro where the culture conditions are and can be carefully controlled and adjusted, it is apparent that the effect in the whole animal or patient is less defined and controllable *in vivo* where the conditions such as the interaction of a complex array of hormones, other growth factors, inhibitors of expression of the gene product, naturally occurring host defense mechanisms and cells interact to modulate overall cell function. Of note in this regard is the reference by Steel (The Lancet) which indicates that even though cyclins affect cell cycle control via cyclin/Cdk complex, not all roads ultimately lead to such a complex and at page 932 indicates that the evidence as of 1994 which is a time contemporary to the filing of the instant application that the evidence is inconclusive, and that p53 may not be the common point in tumorigenesis and its control and that other factors such as growth factors (e.g., TGFβ), cyclins where in perspective, it is a disorder of the whole organism and not simply of cells and genes wherein the instant written description does not indicate how expression of DNA encoding p53 effects the cyclin/Cdk complex. Here, Kamb *et al.* (Science, vol. 264) also indicate at a time contemporary to the filing of the instant application that (page 436) the most common oncogenic mutations are in *HRAS*, found in 10 to 15% of solid tumors" and that the most frequently mutated tumor suppressor gene is the DNA encoding p53. However, "Without a target that is common to all transformed cells, the dream of a "magic bullet" as would be asserted by the (1) broad generic claims, and, (2) the list of tumor cells in claim 9 "that can destroy or revert cancer cells while leaving normal tissue unharmed is improbable". Thus, the instant application is apparently inadequate as to written description in view of the above as the Kamb *et al.* indicate that of the less than a dozen or so tumor suppressor genes now known, it is expected to increase beyond 50 genes and underscores the complexity of growth and control mechanisms that maintain the integrity of normal tissue and that "So far no single gene has been shown to participate in the development of all or the majority of human cancers. Here, using DNA encoding p53 is not apparently going to have any effect on a p16 deletion.

It is also not demonstrated how for example aerosolized preparations are going to cross the blood brain barrier or penetrate parts of the body for treatment of osteogenic sarcomas or central nervous system tumors. Moreover, the present specification presents *in vitro* examples but given the above, there is an indicated uncertainty presented by the above cited references and in at least the Chen *et al.* (Oncogene, vol 6) reference discussed above as to what expression of DNA encoding wild-type p53 would have had in other preexisting tumor cells in an animal or patient. Here, there is

further doubt as Ullrich *et al.* (Oncogene, vol 7) indicate (page 1641) that there may be different p53 mutants that exert a stronger dominant negative effect *in vivo* than other mutant forms of p53 in which case, wild-type p53 may not be able to exert an antiproliferative effect under any circumstances and at page 1642, it is indicated that p53 also has a role in effecting proliferation of cells, thus, there is doubt that effecting expression of wild-type p53 always leads to the same result asserted in the instant specification as Ullrich *et al.* also indicate that in several proliferating human tumors, there are relatively high levels of wild-type p53 and, thus, high levels of wild-type p53 may be necessary but are not apparently always sufficient to effect growth arrest. Thus, even for p53, it is apparent that the effects of over and under expression are unpredictable in different types of tumors and tumor cells and where the above indicated references present differing discussions as to the cells exemplified in the instant specification, there is doubt expressed in the art as to the actual effect of wild-type p53 expression upon/in the tumor cells. Thus, the disclosure and experiments described in the present specification that are all performed *in vitro* would not lead the artisan to extrapolate the *in vivo* experimental conditions and results to the *in vivo* situation in the absence of a demonstrated ability to control time of expression, amount of expression, ability to terminate expression as the instant examples with the glioblastoma multiforme cells are indicated by Saris *et al.* (J. Neurosurg.) as not having any curative therapy (see for example page 513) which is indicative that that one would not have been led to extrapolate the *in vitro* conditions to any curative effect *in vivo*. Moreover, Ullrich *et al.* points to the unpredictability of the results and where unpredictable as the Ullrich *et al.* reference would appear to indicate, the *in vitro* experiments performed in the present application are not likely to be accepted as correlated to or predictive of results obtainable *in vivo* in humans or other animals for all types of neoplasms and neoplastic cells nor do the present specification disclosed *in vitro* experiments appear to reflect a realistic set of parameters as here, the specification does not indicate treating an intact preexisting established tumor in an intact animal. Note that Friedmann (Cancer, Suppl.) indicates that even in model systems, only some of the features of the tumor phenotype can be suppressed by restoration of expression of tumor suppressor genes such as Rb and p53 and that before the phenomenon can serve as a basis for gene therapy of cancer, many conceptual and technical problems must be solved and at page 1814 Friedmann indicates that cancer suppression by a virally delivered gene for the Rb and p53 genes is no assurance that the same will be feasible for other

members of the rapidly growing family of tumor suppressor genes wherein Friedmann indicates at page 1815 that:

> "it is likely that there will be major differences between the suppression of tumorigenicity of grafted genetically modified tumor cells and the reversal of growth of an overt existing tumor in an animal with a significant tumor burden. To our knowledge, no studies have reported the efficient delivery of a vector to a preexisting tumor *in vivo* followed by a significant effect on tumor growth"

as where the present written description falls into this category because there is no *in vivo* demonstration of the same effect as produced *in vitro* for the present claims which encompass besides the p53 exemplified, all wild-type therapy sensitizing genes. Thus, it is not apparent that the *in vitro* data are extrapolatable to the whole animal *in vivo* as required by the absence of appropriate qualifying language in the presently claimed method. The working examples in the present specification used cells *in vitro* where the above references indicate such data are not necessarily directly correlated to what would occur in the whole animal as the none of the cells are correlated to the transfection of primary patient derived tumor cells in view of the fact that clonal cell lines are not the same as the cells in a tumor in an individual as for example the above cited Chen *et al.* (Oncogene, vol. 6) explicitly indicates (page 1799) that even when DNA encoding p53 is expressed, it is apparently ineffective in altering the neoplastic properties of the cell and that the effect of p53 may in fact be dependent upon cell type - i.e., that the effect may be cell type specific and therefore, not have been effective in all types of tumor cells - thus, there is doubt created by the art that the DNA encoding p53 would be effective in all cancers as it is not indicated in the present specification that the DNA coding the therapy sensitizing properties of the p53 are in all DNA that encode a product made from that DNA that effect a therapy sensitizing function.

At page 7, the specification refers to genetic mutations that effect abnormally increased expression of the DNA or increased activity of the product of that DNA and that such activity may be "down regulated" by transdominant-negative mutations. This section of the specification is apparently opposite to that of the discussion at page 3 (for example, lines 25+) which indicate that the purpose is to effect the wild-type cancer sensitizing activity by using a DNA encoding a therapy-sensitizing gene to sensitize a tumor cell to cancer therapy by effecting expression (i.e., an increased amount of the gene product) of that DNA encoding a therapy-sensitizing gene because where the cell(s) have, for example, a wild-type p53 activity but it is produced in higher amounts or has more activity than the wild-type product expressed from the DNA, the cell is, by the definitions in the present application,

sensitized to cancer therapy and down regulating same would by the definitions proffered in the present specification, logically result in a desensitization of the cell(s) to cancer therapies wherein the present specification indicates that the function has been lost from the cell (page 8, lines 11-19). Thus, "down regulation" does not appear to correspond to the examples or the rest of the present application written description.

It is noted that the specification at page 8, indicates "activities" at line 16, however, as pointed out above, the DNA (i.e., the gene) is not an activity, it is a deoxyribonucleic acid polymer. Thus, reference to the gene as an activity (page 8, lines 16-19) is inaccurate. It is noted that *fas*, the retinoblastoma gene, and the gene encoding p53 are indicated, however, the reference to "other tumor suppressor genes and cell regulatory gene, and apoptosis genes" do not explicitly indicate what the specific genes are or whether or not these genes do or do not encode the same therapy-sensitizing function in a protein that sensitizes a tumor cell to cancer therapy which is p53 wherein as indicated the specification, at page 11, Vogelstein *et al.* indicate p53 may, therefore, constitute an oncogenic alteration that increases rather than decreases the sensitivity of tumor cells to antitumor agents whereas the present application indicates that it is restoration of p53 function that accomplishes the effect of sensitization to antitumor agents used in therapy. Thus, there are in view of the above cited art conflicting view points as to the function of p53 under various conditions *in vitro* where the appropriate conditions as controllable and adjustable (i.e., predictably controlled) whereas in the *in vivo* condition, such ability to control the parameters is lost because the individual treated would control the formerly adjustable and controllable parameters, and thus, of the DNA encoding same and where there are conflicting viewpoints in the art, one of ordinary skill in the art would not have been persuaded that the effect of expression of wild-type p53 is identical *in vivo* to the *in vitro* conditions applied in the present application as applied to all types of primary tumors/tumor cells in all types of cells as clearly, the cultured cell lines are not those within the animal or patient and are not apparently all controllable as in cells cultured *in vitro*. Thus, it is not apparent that the effect of the DNA encoding p53 and p53 affect all tumor cells lines in the same manner wherein cell lines are not necessarily the same cells/cell type that would have been treated in the patient which is indicative of the quantity of experimentation needed which in view of conflicting opinions in the art reflect the necessity for experimentation which is undue as the cited references would indicate that there is uncertainty in the knowledge in the field of

cancer therapy as applied to the treatment of same as the effects of p53 as not uniform. In view of the present specification it is not apparent that "delivering wild-type therapy sensitizing gene and activity to a cancer cell is adequately described by the lone example of p53 to only T98G and T98Gp53 cells alone for all types and forms of cancer cells or that such genetic material would have had the same effect *in vivo* as the instant written description in the sentence bridging pages 9-10 indicates that "Expression of wild-type p53 does not affect the growth properties of some tumor cell lines, that is not an indication that *in vivo*, the conditions are so altered that all things react the same way or that all cancers are now equivalent. Thus it is not apparent that the effect of the DNA encoding p53 and p53 affect all tumor cells lines in the same manner wherein cell lines are not necessarily the same primary tumor cells/cell type that would have been treated in the patient as for example where the present specification indicates in example 7 glioblastoma multiforme but it is not clear where and how the DNA for p53 by aerosolized preparation crosses the blood brain barrier wherein there is no readily apparent extrapolation of the parameters as for example, at pages 21-22 of the present specification, indicates typically increasing the dosage levels until the desired effect is achieved, however, it is not apparent what is going to happen nor is it apparent that the dosage of the therapeutic agent would have been reduced in the instance where page 7, of the specification refers to genetic mutations that effect abnormally increased expression of the DNA or increased activity of the product of that DNA and that such activity may be "down regulated" by transdominant-negative mutations (i.e., a mutation, wherein to effect the transdominant mutation and phenotype, one uses a mutant form of the DNA, not the wild-type, which is diametrically opposite to that of restoring the function of the wild-type gene. Where the wild-type gene is expressed, what is the necessity of restoring the function?. This section of the specification is apparently opposite to that of the discussion at page 3 (for example, lines 25+) which indicate that the purpose is to effect the wild-type cancer sensitizing activity by using a DNA encoding a therapy-sensitizing gene to sensitize a tumor cell to cancer therapy because where the cell(s) has for example a wild-type p53 activity but is produced in higher amounts or has more activity than the wild-type product expressed from the DNA, the cell is, by the definitions in the present application, sensitized to cancer therapy and down regulating same would by the definitions proffered in the present specification, logically result in a desensitization of the cell(s) to cancer therapies wherein the present specification indicates that the function has been lost from the cell (page 8, lines 11-19). Thus, the amount of direction and/or guidance presented in the working examples is inadequate as in view of

the foregoing, there are tumors that have intact DNA encoding wild-type p53 (see Chen *et al.* as well as Shaulsky *et al.* wherein Shaulsky *et al.* indicate at page 8982 that while transfection of wild-type p53 interfered with proliferation of colorectal carcinoma that contained a mutated p53 gene, no effect was detected when it was expressed in a colorectal adenoma that contained a wild-type p53 gene, i.e., the effect is not the same in all cells and cancers and where expression has no effect, how is it determined that it lowers or even alters the effect of given dosages of routinely used therapeutics administered to patients - thus, doubt of the universality of such treatment method as claimed is demonstrated) and in example 6 (page 26+), it is not clear what is to be done in this instance and in examples 7-9, the screening assay does not indicate nor demonstrate even one small molecule (not previously known to have the sensitizing effect) that the assay has identified to have therapy sensitizing effect nor does the toxicity testing demonstrate anything nor is it demonstrated as possible to administer that which has not been identified as a therapy synthesizing molecule - i.e. there is undue experimentation to use that which is not known - the unidentified DNA that encodes other wild-type therapy synthesizing genes - which factors that effect unpredictability as evidenced by the contemporary knowledge of the relevant art - which also indicates how the skilled in the art would have assessed the unpredictability of the state of the art - i.e., that it was not predictable because even where the level of skill is quite high, how does it predict the unknown. Moreover, in 1994, a time contemporary to the instant filing, Roemer *et al.* indicate (page 274-275) that:

> "It is unlikely that expression of exogenous p53 through gene transfer will find clinical usefulness for all forms of cancer. Not all tumor cell types show defects in p53 genes. For instance, only approximately 50% of the clinically important breast cancers have mutated p53 or lack p53 expression. Secondly, other types of tumor cells, like cervical carcinomas, may express p53-inactivating oncoproteins such as HPV E6 or, like several soft-tissue sarcomas, may over express cellular factors such as MDM-2 with the potential to bind and inactivate p53. Characteristically, these types of cancer cells rarely show the typical selection against wt p53 expression exhibited by many carcinomas. Consequently, introduction of additional p53 into these cells is unlikely to be effective"

which creates doubt in view of the contemporary knowledge in the art as indicated above at the time the claimed invention was made (i.e., the effective filing date) that persons skilled in the art in view of the foregoing would have found the present written description adequate and enabling or have applied the process for all cancers to all cancer cells for the process which as claimed is applied to all cancers and all cancer cells where the sole apparent indicated method of use is for therapy. Note that Roemer *et al.* indicate at page 270-271 that such therapy with p53 is in 1994 still only the hope of many who study tumor suppression and in the discussion of the Roemer *et al.* reference, it was even suggested (page 280) that if one can put a gene into a cell and get it expressed, why not use a gene that will kill

the cell rather than a gene that converts it back to normal - is not apparently suggestion to use p53 for all cancers and cancer cells. Thus, there is indication that the skilled in the art differ in opinion from the instant specification as to universal application of p53 DNA and at page 281, there is expression of doubt as to even the length of time or permanency of expression of the replaced p53.

In light of the contemporary knowledge in the art wherein Roemer *et al.* (published in 1994) expresses doubt as to the universality of the application of DNA encoding p53 to all cancers, i.e., others expressed that it is unlikely to be effective for all cancers. Note that Roemer *et al.* indicate at page 270-271 that such therapy with p53 is in 1994 still only the hope of many who study tumor suppression and in the discussion of the Roemer *et al.* reference, it was even suggested (page 280) that if one can put a gene into a cell and get it expressed, why not use a gene that will kill the cell rather than a gene that converts it back to normal - is not apparently suggestion to use p53 for all cancers and cancer cells. Thus, there is indication that the skilled in the art differ in opinion from the instant specification as to universal application of p53 DNA and at page 281, there is expression of doubt as to even the length of time or permanency of expression of the replaced p53. Thus, it is apparent that others skilled in the art would not have accepted the assertions of therapeutic utility on the face of the instant written description in the absence of convincing scientific evidence given the doubts expressed in the cited references.

Claims 1-22 are rejected under 35 U.S.C. 112, first paragraph, for the reasons set forth in the objection to the specification.

Claims 1-22 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 1 is indefinite because the where "increasing the effect of a cancer therapy" is recited, the "subjecting said tumor cell to said cancer therapy" does not indicate what is the effect of the therapy nor what that therapy does nor does the recitation of "delivering the "wild-type therapy-sensitizing gene activity" indicate what the effect of that "delivering" accomplishes nor is it indicated how that "delivering" modifies "subjecting said tumor cell to said cancer therapy" wherein it is not clear from the present claim terminology whether or not lethal doses are included or excluded. In claim 1, it is also

not clear what is the "wild-type therapy-sensitizing gene activity" or what is the gene that provides "activity" nor is it clear what is or is not a "gene activity" nor does the claim indicate how an "activity" is delivered. Claim 2 is indefinite because the claim does not indicate what part of the DNA is or is not the "a portion of a therapy-sensitizing protein" and "a portion of a therapy-sensitization gene activity" What part of the *fas* gene (claim 21) corresponds to the DNA encoding p53 (claim 22)?. Claim 3 is indefinite because the claim does not indicate what is or is not the "a portion of a therapy-sensitizing gene" nor what is or is not the "a portion of a cDNA encoding said therapy-sensitization gene activity". Furthermore, claim 3 contains a Markush group via the "or" and the use of "... a portion ..." in the terminology of the claim leaves the species of the claim open ended. Open ended Markush groups are indefinite. In claim 6, it is not clear as to what is or is not "a biological therapy" and what is or is not the bounds of said therapy with regard as to whether it refers to using a biological molecule or an organism exogenous to the individual treated for cancer to effect the method claimed. Claim 9 is also indefinite as there is no antecedent basis of "cells" plural in claim 9 by recitation of "said tumor cell" singular (note the dependence upon claim 1). Note also that claim 9 is also indefinite as it is not clear in the Markush group how head and neck cancer cells are mutually exclusive to and do not overlap esophageal cancer cells as such cells are part of the anatomy forming the neck (see *Ex parte Clark and Summerling*, 174 USPQ 40 (Pat Off Bd Appl 1971) which indicated that Markush group species must be mutually exclusive as it is not clear how "carcinoma cells" without terminology indicating the tissue of origin differ from other specific tissue carcinoma cells) see also leukemia cells, hematopoietic tumor cells, and osteogenic sarcoma cells; and, colorectal carcinoma cells, and anal cancer cells or even how any of the cell types differ from "carcinoma" cells. Claims 10, 12-22 are also indefinite as they contain the indicated "... a portion ...". How much is "a portion"? How many bases are or are not included? What is the sequence of the "a portion". Claim 17 is also indefinite as "aerosolized preparation" is a composition and is not *per se* a step of "... introduced to said tumor cell ...". In claim 21, it is not clear what is "fas" nor what is the therapy that is referred to in the claim. Is it a typographical error or does "fas" refer to a particular gene for which the full spelled out name does not appear in the present specification, in which instance it should be offset from the text such as by italics or underlining, or does it refer to an acronym or an abbreviation in which instance, the full name of same should precede any recitation in the claim?

The following is a quotation of 35 U.S.C. 103 which forms the basis for all obviousness rejections set forth in this Office Action:

> "A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) and (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103, the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103.

Claims 1-11, 17-20 and 22 are rejected under 35 U.S.C. 103 as being unpatentable over Cheng *et al.* (Cancer Res.) taken with Srivastava (US '749), Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2).

Cheng *et al.* disclose suppression of T-cell acute lymphoblastic leukemia (T-ALL) post transfection of T-ALL cells with a vector that effects expression of the p53 gene product (see at least the abstract) and suggest such treatment for therapeutic suppression of the unregulated growth of T-ALL cells by introduction of the DNA encoding p53 into cells in conjunction with autologous bone marrow transplantation regimes in an effort to reduce the frequency of posttransplantation relapse and at page 225, the teaching that expression of the wild-type allele for p53 effected a "powerful suppression of the tumorigenic phenotype *in vivo* (i.e., a correlation of the effects) without evidence of significant toxic effects in the cells. Here, where Cheng *et al.* indicate use of vectors to provide the DNA encoding wild-type p53, it would have been obvious to one of ordinary skill in the art to have used known vectors and processes demonstrated as effective that are known to function *in vivo* for delivery

of known DNA encoding wild-type p53 wherein Srivastava discloses vectors that are indicated as safe for gene therapy (i.e., reduction/elimination of a factor in the potential problem of heterologous DNA effecting unwanted effects which also would have motivated one of ordinary skill in the art to have used the teachings and vectors and modifications thereto such as disclosed in the Srivastava '749 patent which at col 3 indicates the vectors are for bone marrow cells (i.e., like those of the Cheng *et al.* reference) and to have used virus such as an adeno, herpes, or vaccinia virus (see col 3) for delivery of DNA encoding for example p53 or Rb (col 6) for treatment of cancer (col 6).

Here, where Cheng *et al.* refer to bone marrow transplantation regimes, it would have been obvious to anyone of ordinary skill in the art that radiation therapy (as for example Moossa *et al.* at pages 477, 1138, 1140, and 1170), chemotherapy (as for example Moossa *et al.* at pages 527-536, 565-568, 1098, 1140, and 1572), biological therapy (as for example Moossa *et al.* at pages 607-612 using biological response modifiers), cryotherapy (as for example Moossa *et al.* at pages 1098, 1170, 1329, 1368, and 1569-1570), and hyperthermia (as for example Moossa *et al.* at page 1139-1149) are known treatment methods, have been successfully used, and are routine for one of ordinary skill in the art to have used in treating cancers either as single methods or as combined methods in various combinations as well as to have used routine methods for delivery of the therapeutic agent (as for example via an artery (page 590) or a (page 591) body cavity or by IV as for example indicated at page 592) and would have resulted in the process wherein a DNA encoding a tumor sensitizing product would have been delivered to an afflicted individual along with routine known and established appropriate therapies (radiation therapy, chemotherapy, biological therapy, cryotherapy, and hyperthermia therapy in one or more combinations) for treatment of cancers. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Claims 12-18, and 20 are rejected under 35 U.S.C. 103 as being unpatentable over Cheng *et al.* (Cancer Res.) taken with Srivastava (US '749), Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) as applied to claims 1-11, 17-20, and 22 above and further in view of Wu *et al.* (US '320) and Malkin *et al.* and Chen *et al.*

Cheng *et al.* (Cancer Res.), Srivastava (US '749), and Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) and where Srivastava indicate safe vectors, Wu *et al.* disclose a process for *in vivo* delivery (as for example intravenous injection, i.e., a direct injection wherein injection into an artery is an obvious variation of injection into a vein) of DNA to a target cell (see for example col 11, and the abstract as to polylysine) using a complex of asialoglycoprotein to hepatoma cells and for replacement of "defective genes" responsible for inherited diseases as for example where there are familial germline mutations of cancer where mutations in the DNA encoding p53 have been shown to be transmitted via the germline (see Malkin *et al.*, the abstract and pages 1234-1238) and where Cheng *et al.* indicate that providing DNA encoding wild-type p53 to cells that have defective or no expression of p53 with subsequent expression of that DNA encoding wild-type p53 effects reduced tumorigenicity (see page 1803) wherein it would have been obvious to one of ordinary skill in the art to combine the teachings of Cheng *et al.* (Cancer Res.) taken with Srivastava (US '749), Moossa *et al.* with Wu *et al.*, Malkin *et al.* and Chen *et al.* for treatment of cancer and directed delivery of the DNA encoding for example p53 to effect reduced tumorigenicity and reduced frequency of posttransplantation relapse. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Claims 1-15, 17-20 and 22 are rejected under 35 U.S.C. 103 as being unpatentable over Nabel *et al.* (US 470) taken with Wu *et al.* (US 320), Malkin *et al.* (Science), and Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2).

Nabel *et al.* indicate genetic therapy by transforming cells *in vivo* to treat malignancies (col 11-12) by inhibiting tumor cell growth by gene transfer directly into the tumor cells where (1) the transforming DNA induces rejection, regression or both of the tumor (col 12, lines 45+); (2) the vector is a liposome complex and/or conjugated with for example polylysine (col 11, line 15+ and col 14, line 60+) wherein Wu *et al.* disclose a process for *in vivo* delivery (as for example intravenous injection, i.e., a direct injection wherein injection into an artery is an obvious variation of injection into a vein) of DNA to a target cell (see for example col 11, and the abstract as to polylysine) using a complex of asialoglycoprotein to hepatoma cells and for replacement of "defective genes" responsible for inherited diseases as for example where there are familial germline mutations of cancer where mutations in the

DNA encoding p53 have been shown to be transmitted via the germline (see Malkin *et al.*, the abstract and pages 1234-1238) and/or in a virus such as derived from adenovirus, papilloma virus, herpes virus, or parvovirus (col 13); (3) the DNA is for example p53 (col 14 and 18); where (4) the reference indicates that the function of the transforming DNA is in one instance antagonize by overexpression, the function or other activities of a gene in the animal or patient (col 10) such as to suppress an endogenous gene (col 1 of Nabel *et al.* wherein Malkin *et al.* indicate that the endogenous gene is p53 which is defective, it would have been obvious to suppress expression of a defective endogenous p53 gene by replacement with the form of the gene which is not defective and thereby suppress the effect of the defective gene) which is for example a tumor antigen (col 18) indicated as a mutant p53 oncogene that where Malkin *et al.* disclose that p53 mutations are transmitted via the germline in familial breast cancer, sarcomas, and other neoplasms, it would have been obvious to one of ordinary skill in the art from at least the motivating reasons of cancer suppression (Nabel *et al.*) to have used the wild-type p53 to suppress as for example by blocking the effect of the mutant gene by providing the normal function of p53 by using as the DNA the encoding the wild-type p53 to alleviate the effects of the genetic predisposition to certain forms of inherited cancer which would have altered the effect of known routine cancer treatment regimes which would have been obvious to anyone of ordinary skill in the art to do and which treatment regimes included radiation therapy (as for example Moossa *et al.* at pages 477, 1138, 1140, and 1170), chemotherapy (as for example Moossa *et al.* at pages 527-536, 565-568, 1098, 1140, and 1572), biological therapy (as for example Moossa *et al.* at pages 607-612 using biological response modifiers), cryotherapy (as for example Moossa *et al.* at pages 1098, 1170, 1329, 1368, and 1569-1570), and hyperthermia (as for example Moossa *et al.* at page 1139-1149) are known treatment methods, have been successfully used, and are routine for one of ordinary skill in the art to have used in treating cancers either as single methods or as combined methods in various combinations as well as to have used routine methods for delivery of the therapeutic agent (as for example via an artery (page 590) or a (page 591) body cavity or by IV as for example indicated at page 592) and would have resulted in the process wherein a DNA encoding a tumor sensitizing product would have been delivered to an afflicted individual along with routine known and established appropriate therapies (radiation therapy, chemotherapy, biological therapy, cryotherapy, and hyperthermia therapy in one or more combinations) for treatment of cancers. Thus, the claimed

invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

Claim 21 is are rejected under 35 U.S.C. 103 as being unpatentable over either of Cheng *et al.* (Cancer Res.) taken with Srivastava (US '749), Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) as applied to claims 1-11, 17-20, and 22 above; or under 35 U.S.C. 103 as being unpatentable over Nabel *et al.* (US 470) taken with Wu *et al.* (US 320), Malkin *et al.* (Science), and Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) as applied to claims 1-15, 17-20 and 22 above, and further in view of Itoh *et al.* (Cell).

Cheng *et al.* (Cancer Res.), Srivastava (US '749), and Moossa *et al.* (Comp. Text. Oncol., vol. 1 and 2) and here, where Cheng *et al.* discusses using the DNA encoding p53 to effect cancer suppression, it would have been obvious to one of ordinary skill in the art to have also used DNA encoding the Fas antigen (Itoh *et al.* for enhancing apoptosis of cancer cells) for killing cells such as by ionizing radiation (a routinely used cancer therapy (see for example Moossa *et al.*) that effects DNA strand breakage) it would have been obvious to one of ordinary skill in the art that to have killed human carcinoma cells by combination therapy using the DNA encoding the Fas antigen (Itoh *et al.*) because upon treatment with gamma-interferon, the cells produce more Fas antigen and Fas antigen renders such cells susceptible to the killing effect of anti-fas antibody. See for example page 237 of the Itoh *et al.* reference. Thus, it would also have been obvious to one of ordinary skill in the art to have also used the *fas* gene and such application as indicated above would have resulted in the claimed method.

Alternatively, where Nabel *et al.* and Malkin *et al.* (Science) discuss cancer suppression, p53, and genetic therapy with discussion of the familial inheritance, it would have also bee obvious to one of ordinary skill in the art that to have also used DNA encoding the Fas antigen (Itoh *et al.* for enhancing apoptosis of cancer cells) for killing cells such as by ionizing radiation (a routinely used cancer therapy (see for example Moossa *et al.*) that effects DNA strand breakage) it would have been obvious to one of ordinary skill in the art that to have killed human carcinoma cells by combination therapy using the DNA encoding the Fas antigen (Itoh *et al.*) because upon treatment with gamma-interferon, the cells produce more Fas antigen and Fas antigen renders such cells susceptible to the killing effect of

anti-fas antibody. See for example page 237 of the Itoh *et al.* reference. Thus, it would also have been obvious to one of ordinary skill in the art to have also used the *fas* gene and such application as indicated above would have resulted in the claimed method. Thus, the claimed invention was within the ordinary skill in the art to make and use at the time it was made and was as a whole, *prima facie* obvious.

No claim is allowed.

Kriegler is cited as disclosing that for expression in cells or in an animal (page 3) using various control elements and vectors (see for example pages 23-61) into cells for expression DNA wherein it is indicated that adenoviral and retroviral vectors, herpes virus, vaccinia virus, and papilloma viral vectors were known and used in the art.

Inquiry concerning this communication or earlier communications from the examiner should be directed to Christopher Low whose telephone number is (703) 308-2923. Inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Papers related to this application may be submitted by facsimile transmission to Group 1800 via the PTO Fax Center located in Crystal Mall 1 (CM1) and must conform to the notice published in the Official Gazette, 1096 OG 30 (15 November 1989). The telephone number assigned to Art Unit 1804 in the CM1 PTO Fax Center is (703) 308-4312.

CSFL
15 September 1995

Christopher S.F. Low

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